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(54) Abstract Title
Delivery of naked DNA for wound healing

(57) The delivery of naked DNA encoding a protein which modulates wound healing is described. The DNA is not encorporated in a vector but is packaged, for example in a liposome or viral particle. Preferably the wound healiing modulating agent is a growth factor neutralising agent or an agent which blocks growth factor receptors. Such agents may be antibodies against, or peptides which block receptors of, TGF, interleukins, inteferons, PDGF, integrin receptors, GpIIb/IIIa platelet receptors, inhibitors of convertase enzymes or Latency Associated Peptide (LAP). Also, DNA encoding stimulators of Activin and inhibin or a gene product which modulates actin assembly, such as gelsolin, may be used.

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WOUND HEALING AND REGULATING FIBROSIS

The present invention relates to wound healing and also to regulating fibrosis in the treatment of conditions in which fibrosis is a major mechanism of tissue repair or where excessive fibrosis leads to pathological derangement and malfunctioning of tissue.

Wound healing in adults is a complicated reparative process. The healing process begins with the recruitment of a variety of specialised cells to the site of the wound and involves extracellular matrix and basement membrane deposition, angiogenesis, selective protease activity and re-epithelialisation. An important component of the healing process in adult mammals is the stimulation of fibroblasts to generate the extracellular matrix. This extracellular matrix constitutes a major component of the connective tissue which develops to repair the wound area.

The connective tissue that forms during the healing process is often fibrous in nature and commonly forms into a connective tissue scar (a process known as fibrosis).

There is a need to provide medicaments that promote the healing of wounds. For example, it is often desirable to increase the rate of healing in the case of acute wounds (such as penetrative injuries, burns, nerve damage or even wounds resulting from elective surgery), chronic wounds (such as diabetic, venous and decubitus ulceration) or for generally healing compromised individuals (for example the elderly). In these examples, the wounds can severely influence quality of life or even result in death and therefore the rate of healing often needs to be increased as much as is clinically possible. Where the rate of wound healing is increased, there is often an associated increase in scar formation but this may be of secondary importance compared to the desired increase in the rate of healing.

There are however other instances of wound healing in which fibrosis is regarded as a major problem in that the scar tissue which forms is not only unsightly but also causes problems in respect of growth, tissue functioning, movement etc. This is particularly true following injuries to children or following major burns. There are therefore situations where the regulation of scar formation is of primary importance and the rate of healing is only of secondary consideration. Examples of such situations are external wounds (especially of the skin) where excessive scarring may be detrimental to tissue function (for instance skin burns and wounds which impair flexibility of a joint). The reduction of scarring when cosmetic considerations are important (e.g. skin wounds of the face) is also highly desirable. In the skin, hypertrophic or keloid scars (particularly common in afro-Caribbean and mongoloid races) can cause functional and cosmetic impairment

As well as external wounds (such as of the skin), internal scarring or fibrosis can be highly detrimental and specific examples include:

(i) Abdominal or peritoneal adhesions or strictures of the gut which may be life threatening scars or fibrotic conditions.

(ii) Scarring or fibrosis in the central nervous system (e.g. following a stroke or neur. surgery) which often leads to functional impairment and may inhibit neuronal reconnection.

(iii) Scarring or fibrosis in the eye (e.g. following injury or surgery of the cornea) may lead to visual impairment. For instance, scarring or fibrosis of the eye following glaucoma surgery can lead to a failure of the pressure equalising operation and may lead to a return of the disease conditions.

(iv) Fibrosis or scarring of ligaments or tendons can have serious effects on function.

Related to the above is the fact that there are a number of medical conditions in which excessive fibrosis leads to pathological derangement and malfunctioning of tissue. Examples include cirrhosis of the liver, glomerulonephritis, pulmonary

fibrosis, scleroderma, systemic fibrosis, rheumatoid arthritis and proliferative vitreoretinopathy, in addition to wound healing. Systemic fibrosis may occur following wounding, ischaemia or some other pathological damage e.g. post-stroke scarring/ fibrosis in the central nervous system, cardiac scarring / fibrosis following myocardial infarction. There is thus also a need for medicaments which may be used for the treatment of such conditions by regulating (i.e. preventing, inhibiting or reversing) fibrosis or scarring.

Whilst the above considerations mainly apply to conditions of man it will be appreciated that wound healing, scarring and fibrosis can also be problematic in other animals (especially domestic animals such as horses, dogs, cats etc). For instance abdominal wounds or adhesions are a major reason for having to put down horses, as are tendon and ligament damage leading to scarring or fibrosis.

There have been several recent developments relating to wound healing. Some of these developments revolve around the recent understanding that growth factors are intimately involved in the repair of wounded tissue. In particular, members of the Transforming Growth Factor β (TGF-β) superfamily have been found to play an important role in wound healing. Thus, WO-A-9217206 discloses the use of growth factor neutralising agents specific against only fibrotic growth factors in wound healing to inhibit scarring. The growth factor neutralising agent may be specific against TGF-β1, TGF-β2 or PDGF.

Furthermore WO-A-9319769 discloses the use of non-fibrotic growth factors for the healing of wounds or for the treatment of other fibrotic disorders, e.g. liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis and rheumatoid arthritis.

The agents disclosed in the prior art for use in wound healing and treatment of fibrosis may be used in various forms for the desired treatment. Thus, for example,

the agent may be provided as a cream, gel, aerosol, powder, patch, dressing, biopolymer or polymer implant, delay or slow release system, in a solution for irrigation, injection or inhalation, or in a tablet for internal administration.

Whilst the agents disclosed in the prior art for use in wound healing and/or treatment of scaring / fibrosis have perfectly satisfactory activity for their intended purpose, known methods of administering the agents to a relevant tissue have the disadvantage that it is difficult to achieve sustained levels of the active agent at a wound site or site of fibrosis over the course of even a few days because the active agents usually have very short half-lives in vivo. The half-lives of the agents tend to be short for a number of reasons which include:

(i) Degradation by proteases and the like.

(ii) Clearance by binding proteins (e.g. $\alpha 2$ macroglobulin).

(iii) Binding and inhibition of agent activity by extracellular matrix molecules such as decorin and fibronectin.

Furthermore, agents for wound healing and/or treatment of scaring / fibrosis need to be administered in a suitable vehicle and are often provided as a composition comprising the agents and the vehicle. Such vehicles are usually required to be non-inflammatory, biocompatible, bioresorbable and must not degrade or inactivate the active agent (in storage or in use). These requirements mean it can often be difficult to provide a satisfactory vehicle for any given agent.

It is therefore an objective of the present invention to obviate or mitigate the abovementioned disadvantages by providing an improved means of delivering an agent for wound healing and/or treatment of scaring / fibrosis.

According to a first aspect of the present invention there is provided a delivery system for use in a gene therapy technique, said delivery system comprising a DNA molecule encoding for a protein which directly or indirectly modulates wound healing

and/or modulates fibrosis or scarring, said DNA molecule being capable of being transcribed to lead to the expression of said protein.

According to a second aspect of the present invention there is provided the use of a delivery system as defined in the preceding paragraph for use in the manufacture of a medicament for use in wound healing and/or modulation of fibrosis or scarring.

According to a third aspect of the present invention there is provided a method of treating a wound and/or modulating fibrosis or scarring comprising administering to a patient in need of treatment a therapeutically effective amount of a delivery system as defined for the first aspect of the invention.

The delivery systems according to the invention are highly suitable for achieving sustained levels of an active agent at a wound site or site of fibrosis over a longer period of time than is possible for most conventional delivery systems. Protein may be continuously expressed from cells at the wound site or site of fibrosis that have been transformed with the DNA molecule of the invention. Therefore, even if the protein has a very short half-life as an agent in vivo, therapeutically effective amounts of the protein may be continuously expressed from the treated tissue.

Furthermore, the delivery system of the invention may be used to provide the DNA molecule (and thereby the protein which is an active therapeutic agent) without the need to use conventional pharmaceutical vehicles such as those required in ointments or creams that are contacted with the wound.

The delivery system of the present invention is such that the DNA molecule is capable of being expressed (when the delivery system is administered to a patient) to produce a protein which directly or indirectly has activity for wound healing and/or treatment of fibrosis or scarring. By "directly" we mean that the product of gene expression per se has the required activity for wound healing and/or regulating

fibrosis or scarring. By "indirectly" we mean that the product of gene expression undergoes or mediates (e.g. as an enzyme) at least one further reaction to provide an agent effective for wound healing and/or regulating fibrosis or scarring.

The DNA molecule may be contained within a suitable vector to form a recombinant vector. The vector may for example be a plasmid, cosmid or phage. Such recombinant vectors are highly useful in the delivery systems of the invention for transforming cells with the DNA molecule.

Recombinant vectors may also include other functional elements. For instance, recombinant vectors can be designed such that the vector will autonomously replicate in the nucleus of the cell. In this case, elements which induce DNA replication may be required in the recombinant vector. Alternatively the recombinant vector may be designed such that the vector and recombinant DNA molecule integrates into the genome of a cell. In this case DNA sequences which favour targeted integration (e.g. by homologous recombination) are desirable. Recombinant vectors may also have DNA coding for genes that may be used as selectable markers in the cloning process.

The recombinant vector may also further comprise a promoter or regulator to control expression of the gene as required.

The DNA molecule may (but not necessarily) be one which becomes incorporated in the DNA of cells of the subject being treated. Undifferentiated cells may be stably transformed leading to the production of genetically modified daughter cells (in which case regulation of expression in the subject may be required e.g. with specific transcription factors or gene activators). Alternatively, the delivery system may be designed to favour unstable or transient transformation of differentiated cells in the subject being treated. When this is the case, regulation of expression may be less important because expression of the DNA molecule will stop when the transformed cells

die or stop expressing the protein (ideally when the wound, fibrosis or scarring has been treated or prevented).

The delivery system may provide the DNA molecule to the subject without it being incorporated in a vector. For instance, the DNA molecule may be incorporated within a liposome or virus particle. Alternatively the "naked" DNA molecule may be inserted into a subject's cells by a suitable means e.g. direct endocytotic uptake.

The DNA molecule may be transferred to the cells of a subject to be treated by transfection, infection, microinjection, cell fusion, protoplast fusion or ballistic bombardment. For example, transfer may be by ballistic transfection with coated gold particles, liposomes containing the DNA molecule, viral vectors (e.g. adenovirus) and means of providing direct DNA uptake (e.g. endocytosis) by application of plasmid DNA directly to the wounded area topically or by injection.

The protein expressed from the DNA molecule may be one which directly or indirectly provides for wound healing with reduced scarring, one which provides an increase in the rate of wound healing whilst possibly resulting in increased scar formation or one which serves to regulate (inhibit, prevent or reverse) fibrosis.

In a first embodiment of the invention, the protein may be a growth factor neutralising agent or agents specific against only fibrotic growth factors. The growth factor neutralising agent may be a growth factor neutralising antibody, for example antibodies to TGF-ß1, TFG- ß2, PDGF, IFNγ or IL-1.

The growth factor neutralising agent may be a growth factor receptor blocking agent, for example a peptide containing the receptor binding site of the growth factors TGF-ß1, TFG- ß2, PDGF, IFNγ or IL-1

The growth factor neutralising agent may also comprise a molecule which binds to the growth factor to inhibit receptor binding. For example when the growth factor is selected from TGF-ß1, TFG-ß2, PDGF, IFNγ or IL-1, the molecule may be selected from Decorin, Biglycan, Fibromodulin, Lumican, Betaglycan, soluble type II TFG-ß Receptor and fragments or derivatives of these molecules which have binding affinity for the growth factors.

The growth factor neutralising agent may be an antisense oligonucleotide or ribozyme(s) to growth factor mRNA which both act to prevent mRNA from being translated.

The growth factor neutralising agent may also be a soluble form of the receptor or the growth factor binding domain of the receptor.

The growth factor neutralising agent may also be an aptmer which binds and neutralises the growth factor.

This embodiment of the invention is useful for inhibiting scar tissue formation during healing of wounds.

Examples of gene products which may be used in accordance with the first embodiment of the invention are disclosed in WO-A-92/17206.

In a second embodiment of the invention, the protein is a non-fibrotic growth factor which may, for example, be TGFß-3, FGF-1, FGF-2, IL-4 or IL-10. Such products are useful particularly for preventing, inhibiting or reversing fibrosis. If desired, the gene product used in the second embodiment of the invention may be co-expressed with at least one anti-fibrotic agent, for example anti-TGFß-1/TGFß-2.

This embodiment of the invention is useful for inhibiting fibrosis during the healing of wounds and in other fibrotic conditions and disorders.

Further details as to gene products which may be used in accordance with the second embodiment of the invention are disclosed in WO-A-93/19769.

In accordance with a third embodiment of the invention the protein is an agent which is capable of affecting the quantity of active growth factor or a protein associated therewith in a wound site at which the gene product is expressed. The agent may, for example, be specific to a non-fibrotic growth factor, e.g. selected from FGF-1, FGF-2, FGF-7, EGF, TGFα, IL-4, IL-10, IL-12, IL-17 or TGF-β_3. Alternatively, the agent may be specific to a fibrotic growth factor, e.g. TGF-β_1, TGF-β_2, PDGFAA, PDGFBB, PDGFA, a member of the CTGF family, IL-1, IL-2, IL-6, IL-8 and TFNα.

This embodiment of the invention may be used to promote the healing of wounds or fibrotic disorders with reduced scarring.

Further details relating to the third embodiment of the invention are given in WO-A-95 26203, the disclosure of which is incorporated herein by reference.

In a fourth embodiment of the invention, the gene product may be IL-4 or IL-10 or a fragment or a partially modified form thereof. By "fragment or partially modified form thereof" is meant a fragment or partial modified form of IL-4 or IL-10 which retains the anti-inflammatory healing functionality of IL-4 or IL-10.

IL-4 and IL-10 as well as fragments and partially modified forms thereof promote the healing of wounds or fibrotic disorders with reduced scarring as disclosed more fully in PCT/GB96/01930, the disclosure of which is incorporated herein by reference.

In a fifth embodiment of the invention the gene product is a soluble betaglycan or a fragment or an analogue thereof which may be used for the healing of wounds or fibrotic disorders with reduced scarring. By "fragment or analogue" is meant a molecule which is capable of binding to TGF-β_2 performing the same role as soluble betaglycan. The "fragment or analogue" may, for example, comprise at least the TGF-β binding fragment of soluble betaglycan.

This embodiment of the invention is useful for the treatment of wounds or fibrotic disorders with reduced scarring.

Reference is made to PCT/GB 96/01840 for further disclosure relating to the use of soluble betaglycan or fragments or analogues thereof, the disclosure of GB 9516073.5 being incorporated herein by reference.

In sixth embodiment of the invention, the protein is an inhibitor of Interferon-γ (IFN-γ).

The inhibitor may, for example, be a neutralising antibody. Alternatively, the inhibitor may be anything which inhibits IFN-γ from interacting with its receptor. It may, for example, be a molecule which mimics the IFN-γ receptor binding sequence and which binds to the receptor but does not activate it, thereby competitively inhibiting the binding of IFN-γ to the receptor and inhibiting the activation of the receptor.

This embodiment of the invention is useful for promoting the healing of wounds or fibrotic disorders with reduced scarring.

In an seventh embodiment of the invention, the protein may be a stimulator of IFN-γ, i.e. an agent which increases the quantity or the efficacy of active IFN-γ at a

site. This may be IFN-γ itself or an analogue of IFN-γ. Alternatively, it may be an inhibitor of IFN-γ metabolism.

This embodiment of the invention is useful for promoting the healing of chronic wounds.

Further details relating to the sixth and seventh embodiments of the invention are disclosed in WO 97/07136, the disclose of which is incorporated herein by reference.

In a eighth embodiment of the invention the protein is an inhibitor of activation of at least one integrin receptor.

The inhibitor may bind to at least one receptor but not activate it.

The inhibitor may comprise an antibody. It may comprise an neutralising antibody. The antibody may bind specifically to at least one integrin receptor. It may bind specifically to the RGD peptide or an analogue thereof.

The inhibitor may comprise at least the RGD peptide or an analogue thereof.

The inhibitor may be any form of inhibitor which inhibits the activation of at least one integrin receptor. It may, for example, be a neutralising antibody specific to the RGD peptide of integrins, it may be a neutralising antibody specific to the integrin receptor, or it may contain the RGD peptide or an analogue (e.g. a RGDS peptide or a mimitope of RGD) thereof which will bind to the integrin receptor and prevent the natural ligand from binding to it.

The receptor may be the GpIIb/IIIa platelet receptor. Therefore the inhibitor may be a GpIIb/IIIa platelet receptor inhibitor. The inhibitor may also comprise an RGD peptide or an analogue thereof.

The inhibitor may inhibit the binding of TGF-β_1 and/or platelets or leukocytes to fibrin and/or fibrinogen and/or fibronectin. It may for example be a fibrinogen receptor antagonist.

This embodiment of the invention is useful for the healing of wounds or fibrotic disorders with reduced scarring.

Further details relating to the eighth embodiment of the invention is given in PCT/GB 96/02366, the disclosure of which is incorporated herein by reference.

In accordance with a ninth embodiment of the present invention, the gene product is an inhibitor of at least one convertase enzyme.

The inhibitor of the convertase enzyme may be a serine protease inhibitor.

This embodiment of the invention is useful for promoting the healing of wounds or fibrotic disorders with reduced scarring.

Further details relating to the ninth embodiment of the invention are given in GB 9620048.0, the disclosure of which is incorporated herein by reference.

In accordance with a tenth embodiment of the present invention, the protein may be a stimulator of Activin and/or Inhibin.

By "stimulator" is meant anything which may stimulate the quantity or efficacy of active activin and/or active inhibin at a site. This may be activin or inhibin

itself or an analogue thereof. Such an analogue may, for example, have a longer half-life than activin or inhibin, or it may have a different binding affinity for its receptors. A fragment may comprise at least that part of activin or inhibin which is required to allow it to stimulate its receptors. Alternatively, it may, for example, be an inhibitor of activin metabolism or it may be a stimulator of activin synthesis. For example, it may be analogue of a fragment of activin or inhibin which is bound by a degraditive enzyme. It may be a mimotope made to a fragment of activin or inhibin which is bound by an enzyme which degrades it. Such a mimotope combined to the receptor site of the enzyme, competitively inhibiting the binding of activin or inhibin (as appropriate) to the enzyme and thereby inhibiting is degradation.

The stimulator may be an antagonist of an agonist of Activin and/or Inhibin. For example, the stimulator may be an antagonist of Follistatin.

This embodiment of the invention is useful for promoting the healing of wounds and fibrotic disorders with reduced scarring.

Further details regarding the tenth embodiment of the invention are given in PCT/GB 96/02559, the disclosure of which is incorporated herein by reference.

In accordance with a eleventh embodiment of the present invention the gene product is one which modulates actin assembly and organisation. The product may for example be Gelsolin, Villin, CaPG, adseverin, flightless-1, advillin or derivatives thereof.

This embodiment of the invention is useful for increasing the rate of wound healing as well as improving scar quality.

Further details regarding the eleventh embodiment of the invention are disclosed in U.K. Patent Application No. 9625148.3, the disclosure of which is incorporated herein by reference.

In accordance with an twelfth embodiment of the present invention the protein may be an agent which inhibits the activity of Interleukin-6.

Suitable inhibitors of IL-6 activity and thereby preferred proteins for use according to the twelfth embodiment of the invention include IL-6 Receptor antagonists (compounds which inhibit receptor activation by IL-6); compounds that disrupt signalling mediated by IL-6 (e.g. inhibitors of second messenger production, kinase inhibitors or modulators of gene expression); enzymes that specifically degrade IL-6 and inhibitors of IL-6 synthesis, neutralising antibodies to IL-6 (which would normally be high affinity antibodies used at a high concentration because low affinity/low concentrations of neutralising antibody are known to act as carriers and protective agents and so potentiate the activity of IL-6 (Heremans et al. Eur. J. Immunol. 22 p2395-2401, 1992), antisense oligonucleotides or ribozymes to IL-6, oligonucleotide aptmers which bind to and neutralise IL-6 or its receptor, molecules which bind to IL-6 and increase its clearance from a wound site.

The most preferred compounds for use as gene products for use according to the fifteenth embodiment of the invention are IL-6 Receptor antagonists and disrupters of IL-6 signalling.

This embodiment of the invention is useful for reducing fibrosis in wound healing and treatment of fibrotic disorders.

Further details relating to the twelfth embodiment of the invention are given in U.K. Patent Application No. 9702944.1.

In accordance with a thirteenth embodiment of the invention the protein is Latency Associated Peptide or a functional analogue thereof.

This embodiment of the invention is useful for promoting wound healing.

Further details relating to the thirteenth embodiment of the invention are given in U.K. Patent Application No. 9702943.3.

In accordance with a fourteenth embodiment of the invention the protein is Insulin Like Growth Factor II or a functional analogue thereof.

This embodiment of the invention is useful for promoting the rate of wound healing and for reducing or preventing scar formation and fibrosis.

CLAIMS

1. A delivery system for use in a gene therapy technique, said delivery system comprising a DNA molecule encoding for a protein which directly or indirectly modulates wound healing and/or modulates fibrosis or scarring, said DNA molecule being capable of being transcribed to lead to the expression of said protein.

2. A delivery system as claimed in claim 1 wherein the protein is a growth factor neutralising agent or agents specific against only fibrotic growth factors preferably TGFß-1, TGFß-2 or PDGF.

3. A delivery system as claimed in claim 1 wherein the protein is a non-fibrotic growth factor preferably TGFß-3.

4. A delivery system as claimed in claim 1 wherein the protein is an agent which is capable of affecting the quantity of active growth factor or a protein associated therewith in a wound site.

5. A delivery system as claimed in claim 1 wherein the resultant protein is IL-4 or a fragment or a partially modified form thereof.

6. A delivery system as claimed in claim 1 wherein the protein is IL-10 or a fragment or a partially modified form thereof.

7. A delivery system as claimed in claim 1 wherein the protein is an inhibitor of Interferon-γ.

8. A delivery system as claimed in claim 1 wherein the protein is a stimulator of Interferon-γ.

9. A delivery system as claimed in claim 1 wherein the protein is an inhibitor of activation of at least one integrin receptor preferably an inhibitor of the GpIIb/IIIa platelet receptor.

10. A delivery system as claimed in claim 1 wherein the protein is an inhibitor of at least one convertase enzyme.

11. A delivery system as claimed in claim 1 wherein the protein is stimulator of Activin and/or Inhibin.

12. A delivery system as claimed in claim 1 wherein the protein is one which modulates actin assembly and organisation preferably gelsolin.

13. A delivery system as claimed in claim 1 wherein the protein is an agent which inhibits the activity of Interleukin-6.

14. A delivery system as claimed in claim 1 wherein the protein is a Latency associated peptide or a functional analogue thereof.

15. The use of a delivery system according to any preceding claim for use in the manufacture of a medicament for use in wound healing and/or modulation of fibrosis or scarring.

16. A method of treating a wound and/or modulating fibrosis or scarring comprising administering to a patient in need of treatment a therapeutically effective amount of a delivery system according to any one of claims 1 - 15.

The Patent Office

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Application No:	GB 9709354.6	**Examiner:**	Dr J Houlihan
Claims searched:	1-15	**Date of search:**	14 August 1997

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Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA) C3H (HB7P)

Int Cl (Ed.6): A61K 48/00

Other: ONLINE: WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	WO 97/00957 A1	(HARVARD COLLEGE) page 31 line 8-page 33 line 24	1, 4 & 15 at least
X	WO 96/39497 A1	(HUMAN GENOME SCIENCES INC.) page 4 lines 6-11 & 18-27; page 27 lines 22-29; pages 44-46 Example 4	1, 4 & 15
X	WO 96/39421 A1	(HUMAN GENOME SCIENCES INC.) page 4 lines 18-35; page 25 lines 5-19; pages 38-39 Example 2	1, 2, 4 & 15
X	WO 96/25178 A1	(UNI. OF UTAH) Whole document	1-4 & 15
X	WO 96/17063 A1	(VICAL INC.) page 4 lines 20-24; page 25 line 32-page 26 line 32	1 & 4
X	WO 95/09241 A1	(TRANSGENE S.A.) page 15 lines 4-8 & 16-22	1, 4, 5 & 13
X	WO 94/22487 A1	(THOMAS JEFFERSON UNI.) page 3 lines 16-28; page 4 lines 12-33	1, 4 & 5 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

The Patent Office

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Application No: GB 9709354.6 **Examiner:** Dr J Houlihan
Claims searched: 1-15 **Date of search:** 14 August 1997

Category	Identity of document and relevant passage		Relevant to claims
X	WO 93/22431 A1	(BAYLOR COLL. MED.) page 5 lines 19-29; page 13 lines 17-28; page 22 Example 7; Claims 29 & 37	1-4 & 15 at least
X	WO 93/13807 A1	(GEORGETOWN UNI.) page 2 lines 9-12; page 20 lines 4-7	1, 4 and 15 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.